

Phenotypic differences in hiPSC NPCs derived from patients with schizophrenia.

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Public Summary:

When skin cells are reprogrammed into stem cells, and then differentiated into brain cells, the brain cells generated remain immature and are most similar to those found in first trimester fetuses. Therefore, when we use this technique to generate brain cells from patients with schizophrenia, we should be aware that we are more accurately studying disease predisposition, rather than schizophrenia, per se. We performed discovery-based genome-wide analysis of the RNA and proteins in control and schizophrenia brain cells, in order to better understand how they differ. Schizophrenia brain cells showed abnormal gene expression and protein levels related to cytoskeletal remodeling and oxidative stress. From this we predicted, and subsequently confirmed, aberrant migration and increased oxidative stress in these cells. We believe that stem cell derived brain cells are a valuable tool with which to study the developmental mechanisms contributing to predisposition for schizophrenia.

Scientific Abstract:

Consistent with recent reports indicating that neurons differentiated in vitro from human-induced pluripotent stem cells (hiPSCs) are immature relative to those in the human brain, gene expression comparisons of our hiPSC-derived neurons to the Allen BrainSpan Atlas indicate that they most resemble fetal brain tissue. This finding suggests that, rather than modeling the late features of schizophrenia (SZ), hiPSC-based models may be better suited for the study of disease predisposition. We now report that a significant fraction of the gene signature of SZ hiPSC-derived neurons is conserved in SZ hiPSC neural progenitor cells (NPCs). We used two independent discovery-based approaches-microarray gene expression and stable isotope labeling by amino acids in cell culture (SILAC) quantitative proteomic mass spectrometry analyses-to identify cellular phenotypes in SZ hiPSC NPCs from four SZ patients. From our findings that SZ hiPSC NPCs show abnormal gene expression and protein levels related to cytoskeletal remodeling and oxidative stress, we predicted, and subsequently observed, aberrant migration and increased oxidative stress in SZ hiPSC NPCs. These reproducible NPC phenotypes were identified through scalable assays that can be applied to expanded cohorts of SZ patients, making them a potentially valuable tool with which to study the developmental mechanisms contributing to SZ. Molecular Psychiatry advance online publication, 1 April 2014; doi:10.1038/mp.2014.22.

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